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SPECIAL ARTICLE

Prevention and treatment of child and adolescent depression: challenges and opportunities

B. Vitiello*

National Institute of Mental Health, Bethesda, MD, USA

Objective. To examine the current theoretical rationale and empirical evidence for preventing and treating major depressive disorder in childhood and adolescence.

Methods. Selective review of recent controlled investigations on the efficacy and safety of preventive and treatment interventions.

Results. Even more than in adults, pediatric clinical trials in depression are dominated by symptomatic improvement with non-specific clinical contact (on average, 50% 'placebo response'). The additional benefit of specific psychotherapeutic or pharmacological treatment is on average modest. Antidepressant medication is effective in speeding up improvement, but more than a third of patients do not reach full remission even after prolonged treatment. The advantage of routinely combining medication with cognitive-behavioral therapy (CBT) is unclear. Depressed suicidal adolescents can benefit from CBT and medications. CBT can protect high-risk youths from developing a depressive episode.

Conclusions. Effective interventions to prevent and treat depression in youth exist, but their therapeutic benefit appears to be, on average, small, possibly due to the clinical heterogeneity subsumed under the current diagnostic construct of depressive disorder. More specifically, targeted interventions tailored to individual clinical and biological characteristics may result in greater effectiveness and overall efficiency.

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Introduction

Depression is one of the main causes of disability across the lifespan (Mathers *et al.* 2005; Kessler *et al.* 2009), and in about 25% of the cases has onset by age 19 (Kessler *et al.* 2005). Difficult to identify before age 6, major depressive disorder has an estimated point prevalence of about 1–2% in elementary school years, and becomes much more common with puberty, achieving a rate of 4–6% in adolescence (Merikangas *et al.* 2010). Puberty represents a turning point in the phenomenology of depression, as also indicated by the change in the male:female prevalence ratio, which is 1:1 before puberty and 1:2 afterwards.

Depression has considerable morbidity in adolescence, impairing social and academic functioning and increasing the risk for substance abuse and suicidal behavior. In the U.S.A., mood disorders rank first among the causes of pediatric hospitalization between 13 and 17 years (Owens *et al.* 2003), and constitute a major risk factor for suicide, which is the third leading cause of death between 15 and 19 years (Centers for Disease Control and Prevention, 2006). In recent years, the diagnosis of depression has become more commonly made in youth, due to an increased awareness of the problem, at least in the U.S.A. There is, however, no convincing evidence that the actual prevalence of depression in the population has been increasing over time (Costello *et al.* 2006).

If the importance of preventing and treating mood disorders is undisputed, there is considerable controversy over the effectiveness and safety of the currently available therapeutic interventions for children and adolescents. This article examines the theoretical rationale and empirical evidence for early prevention and treatment of major depressive disorder in light of the most recent research findings.

Diagnosis of depression in childhood and adolescents: How valid? How informative?

An accurate identification of depression and its antecedents is a prerequisite for developing interventions. The current diagnostic construct of depression was first developed for adults and later applied to

* Address for correspondence: Dr. B. Vitiello, National Institute of Mental Health, Room 7147, 6001 Executive Blvd., Bethesda, MD 20892-9633, USA.
(Email: bvitiell@mail.nih.gov)

adolescents and children. The lack of a biological marker for depressive disorder makes the diagnosis entirely dependent on clinical phenomenology and clinical judgment. Because the distribution of depressive symptoms in the population follows a continuous curve without any obvious point of inflection, the definition of depressive disorder relies on a conventional threshold of symptoms in the presence of dysfunction (Regeer *et al.* 2006). This diagnostic approach, whose limitations are apparent, but for which there is currently no practical substitute, results in a heterogeneous category that conveys little information about course, prognosis and treatment implications. In this nosological context, it is hardly surprising that any generalization about treatment effectiveness is difficult to make, and that clinical trials have been marred by high rates of placebo response.

However, despite the problems with the current nosology, the diagnosis of depression retains a clinical value also in childhood and adolescence. With the help of structured and semi-structured interviews, the diagnosis has both inter-rater and test–retest reliability. Prospective studies have documented continuity across life, as depressed children are at increased risk for depression in adolescence and then in adulthood. This relationship is not inevitably deterministic, and both homotypic (i.e. depression leading to depression) and heterotypic (i.e. anxiety leading to depression and vice versa) continuity can occur (Costello *et al.* 2003). The data are suggestive of a common underlying diathesis toward anxiety–depression, whose clinical manifestations can vary in time within the same individual. The frequent association of depression with other conditions, such as disruptive behavior disorders and substance abuse, adds further complexity. In fact, the prognosis of adolescent depression is substantially worse when it is associated with comorbid conditions (Copeland *et al.* 2009). Finally, an additional challenge in early life is the diagnostic uncertainty surrounding the proper nosological meaning of major depressive episode, as this may be the first manifestation of a bipolar disorder whose manic component is yet to emerge.

In evaluating the effectiveness of therapeutic interventions for child and adolescent depression, it is important to be mindful of the limitations of the nosological context in which these interventions were developed and tested.

Prevention of depression in youth: Is it possible? Is it cost-effective?

The theoretical rationale for trying to prevent depression is compelling, when considering that the personal and societal burden of this illness is considerable and that current treatments, even when implemented according to best practice, take weeks to reduce symptoms, months to restore functioning and are ineffective in about a third of the patients. Thus, even if depression could be promptly identified and treated with state-of-the-art interventions, it would still be impossible to avert its burden completely, hence, the appeal of prevention. This rationale is especially applicable to early prevention, in childhood and adolescence, because this would maximize any beneficial impact on the course of illness across the lifespan. There is evidence that high levels of psychiatric symptoms in childhood are powerful predictors of psychopathology later in life. For example, in a Finnish sample, a simple screening of 8-year-old children conducted by parents or teachers could identify 80% of the males who would commit, or seriously attempt, suicide by age 25, and for every 20 boys who screened positive, one displayed lethal or near-lethal suicidal behavior in the following 17 years (Sourander *et al.* 2009). These are clear indicators that early identification of the precursors of severe psychopathology is possible.

Different approaches to the prevention of depression can be envisioned. A number of universally implementable strategies, such as preventing bullying in schools, increasing physical activity and fighting obesity, can have a general benefit on the health and mental health of children, and these positive effects would likely extend also to reducing stress, anxiety and depression. Universal interventions are to be considered, and their cost effectiveness evaluated, in the broader context of enhancing general health, with prevention of depression being just one component. At this time, no controlled investigations have evaluated with sufficient statistical power the potential impact of universal interventions on health and depression.

Another approach has been to focus on interventions targeted at youths at high risk for developing an episode of major depression. History of depression in the first-degree family, personal history of previous depression, presence of anxiety or subsyndromal depressive symptoms, each contributes to elevate the risk for subsequent depression. Adolescents with subsyndromal depression, for example, have an increased risk for depression and suicidal behavior in adulthood (Fergusson *et al.* 2005). Preventive intervention for high-risk youths mainly consists of cognitive-behavioral therapy (CBT), typically provided in group sessions (Clarke *et al.* 2001).

A course of 8 weekly group CBT sessions followed by 6 monthly continuation sessions significantly decreased the incidence of depressive episode from 33% (with usual care) to 21% (Garber *et al.* 2009).

The difference in rates corresponds to a number needed to treat (NNT) in order to prevent one case of depression of 9. This NNT compares favorably with the NNT for antidepressant treatment in adolescent depression, which is on average 10 (Bridge *et al.* 2007). In this study, the presence of depression in at least one of the parents had a significant moderating effect on the outcome: youths whose parents were depressed did not benefit from the preventive intervention. These data are consistent with other reports that parental depression influences the mood of the offspring. During treatment of depressed adults, remission of maternal depression was accompanied by a reduction in the child's depressive symptoms; on the contrary, failure to remit was associated with worsening in the child's outcome (Weissman *et al.* 2006). Thus, it appears that in order to properly address depression during development one must take into account the mental health of the parents and coordinate treatment of the child and family in an integrated and comprehensive manner.

If there is evidence that depression can be prevented in high risk youth in the short and intermediate term (i.e. within about one-year time frame), it remains to be determined whether the preventive effect extends into future years. It is theoretically plausible that CBT should provide enduring skills that could protect youths from developing depression (Hollon *et al.* 2006). Empirical evidence, however, is still lacking, and long-term, prospective studies will be needed to address this issue.

Based on the available data, it appears that preventive interventions for adolescent depression can be cost effective. Compared with usual care, a brief, 15-session, group CBT intervention has an estimated incremental cost of $9275 per quality-adjusted life-year (95% CI, −$12 148 to $45 641) (Lynch *et al.* 2005). Recently, there has been increasing interest in Web-based applications for delivering CBT also to adolescents, and these approaches, if found effective, could translate into an even greater cost effectiveness. Furthermore, a better understanding of the gene environment interaction processes may allow a more precise identification of high-risk individuals, so that more targeted and efficient preventive strategies may be developed.

Treatment of depression in childhood and adolescence: How effective? How safe?

There is debate on the therapeutic value of treatment interventions for children and adolescents with depression. An episode of depression usually lasts for months, sometimes years. Even when depression eventually abates, residual symptoms often persist and functional recovery remains incomplete. Furthermore, recurrence is common. Thus, despite the tendency of depression toward spontaneous improvement in at least one-third of the cases, especially those with milder symptoms, there is general agreement that youths with moderate-to-severe depression should be treated (Birmaher *et al.* 2007). A number of controlled clinical trials have shown that both psychotherapeutic and pharmacological interventions can be effective for children aged between 7 and 18 (Weisz *et al.* 2006; Bridge *et al.* 2007). In particular, CBT and interpersonal therapy have been found better than non-specific support or family therapy, and two antidepressant medications have been approved by the U.S. Food and Drug Administration for the treatment of depression during development: fluoxetine for age 7–17 and escitalopram for age 12–17. However, because patients with depression often improve with non-specific clinical contact ('placebo response'), the treatment effect (i.e. the difference between specific treatment and control) is, on average, small. When the difference is expressed in standard deviation units (Cohen's effect size), CBT has an average effect size of 0.34 and the selective serotonin reuptake inhibitors (SSRIs) of 0.25, with an NNT around 10 for SSRIs (Bridge *et al.* 2007). These are small effect sizes, based on conventional standards, and indicate that current treatments have, on average, a modest therapeutic effect. The high placebo response is in good part responsible for this small effect. The placebo response is the cumulative effect of a number of factors, such as spontaneous remission, expectation of improvement (or placebo effect proper), patient recruitment strategies and mathematical regression to the mean. As in adults, also in children, the milder is the depression, the greater is the placebo response, at least in pharmacological trials (Bridge *et al.* 2009). Moreover, placebo response is greater in younger children, probably because their mood tends to be more reactive to non-specific support than later in life.

When considering meta-analyses of pediatric-controlled trials in depression, it should be noted that there is heterogeneity among trials, and that, while many studies could not detect a statistically significant difference between active treatment and placebo, some trials showed the presence of a clear-cut effect. For example, the Treatment for Adolescents with Depression Study (TADS), a U.S. publicly funded multisite placebo-controlled trial that compared fluoxetine, CBT, and their combination, found a response rate of 61% on fluoxetine *v.* 35% on placebo, with an effect size of 0.7, after 12 weeks of treatment (TADS, 2004). These rates correspond to an NNT of 4, which is very favorable. The TADS participants suffered

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from a prolonged depressive disorder, with a median duration of 40 weeks, and had a high rate of comorbidity (52%), clinical characteristics that might have contributed to a lower placebo response than in other trials. The TADS also found that, for the population of moderately to severely depressed adolescents, CBT was not more effective than non-specific clinical contact with pill placebo. But some patients, such as those with milder depression, more cognitive distortion, or higher socio-economic status, did quite well on CBT, thus supporting a tailored approach to the individual needs of adolescents with depression (Curry *et al.* 2006).

More difficult is to interpret the comparison between fluoxetine (which was delivered under double-blind conditions) and the combination of fluoxetine and CBT (delivered openly, with outcomes assessed by independent blinded evaluators) (March & Vitiello, 2009). While the combination was associated with a more rapid symptomatic improvement, the response rate at 12 weeks (71%) was not statistically different from fluoxetine alone (61%). Furthermore, in the following 6 months of treatment, the response rate on all the active treatment (fluoxetine, CBT, and combination) gradually converged to final rates between 81 and 86% at 9 months (TADS, 2007). These data indicate that SSRI treatment with fluoxetine speeds up improvement, but the distal outcome may not be influenced by the type of treatment.

Other considerations, however, are in order. Antidepressant treatment has been found, rather unexpectedly and counter-intuitively, to be associated with a higher risk of suicidal events, such as suicidal ideation and suicide attempts (but not complete suicide!), compared to placebo (Hammad *et al.* 2006). In a meta-analysis of 13 trials in depression, the average rate of suicidal events was 3% on antidepressant and 2% on placebo (Bridge *et al.* 2007). In the TADS, over the 9-month period of treatment, the rate was 14.7% in the fluoxetine alone group, 6.3% in the CBT group and 8.4% in the combination group (TADS Team, 2007). If combining CBT with medication reduces the risk of suicidal events, then it would be advantageous to use this more intensive treatment approach rather than medication alone. The higher cost of CBT would be compensated by the lower risk of suicidal events, an outcome that is often associated with expensive emergency interventions and hospitalization (Domino *et al.* 2009). The current data, however, are not univocal in supporting the use of combined treatment (Vitiello, 2009). A U.K. randomized trial of fluoxetine alone *v.* the combination fluoxetine/CBT in adolescent depression could not find any differences between the two treatment modalities in either efficacy or suicidality, thus raising doubts about the value of systematically adding CBT to medication (Byford *et al.* 2007; Goodyer *et al.* 2007).

The ultimate goal of treatment is remission of the depressive episode and full recovery of functioning. Not surprisingly, achieving these outcomes takes longer than simply decreasing depressive symptoms (Vitiello *et al.* 2006). With treatment, the chance of reaching remission by 9 months is estimated to be about 60% (Kennard *et al.* 2009). Most youths who reach remission maintain this depression-free status for at least 1-year (TADS Team, 2009), but about one-fourth relapse (Vitiello *et al.* 2010). Unfortunately, there is no evidence that having received CBT confers *per se* protection again relapse. However, there are suggestions that adding continuation CBT sessions after acute improvement may decrease the risk of relapse (Kennard *et al.* 2008). Continuing antidepressant treatment after acute response also decreases the risk of relapsing (Emslie *et al.* 2008).

Even with state-of-the-art treatment, about a third of depressed youths do not improve after first-step treatment and therefore require second-step interventions. A recently reported trial compared different second-step interventions for depressed adolescents who had not improved on an adequate course of SSRI (Brent *et al.* 2008). These adolescents were randomly assigned to switching to another SSRI or to venlafaxine, with or without CBT. At 12 weeks, those randomized to combined antidepressant/CBT had a greater rate of improvement (55%) than those treated just with medication (40%). However, contrary to TADS, CBT did not decrease the risk of suicidality compared to medication. The cumulative remission rate was 39% after 24 weeks of treatment and 61% by 72 weeks, thus confirming that, for at least one-third of cases, adolescent depression persists, although attenuated, over time (Emslie *et al.* 2010; Vitiello *et al.* 2010).

The finding that antidepressant use raised the risk for suicidal events compared to placebo has raised questions as to the possible mechanisms for this paradoxical effect. It has been proposed that SSRI may cause behavioral activation in some individuals, with increase in anxiety and mood instability, which in turn would lead to suicidal thoughts and behaviors. The data, however, do not seem to support this hypothesis, as most suicidal events occur in the context of persisting depression and insufficient improvement, but are not preceded by clinical signs of behavioral activation (Vitiello et al. 2009*a*, *b*). It must be pointed out that no complete suicide occurred in the antidepressant clinical trials in children and adolescents, and that epidemiological data actually suggest that increased use of antidepressants in the community was accompanied by a decreased incidence of suicide (Gibbons *et al.* 2006).

A particularly important issue is how to treat adolescents who are depressed and are at especially high risk for suicide due to a recent suicide attempt. Suicide is multidetermined, and various factors can contribute to it (Vitiello & Pearson, 2008). Having recently attempted suicide considerably increases the risk of attempting it again in the near future, with estimated rates of recurrence as high as 30% within the following 6 months. Depression is an independent risk of suicide. Thus, the combination of being depressed and having recently attempted suicide confers a particularly high risk for recurrence. Little empirical evidence currently exists to guide treatment for these patients, who have been systematically excluded from clinical trials on safety and ethical ground. Recently, a pilot, non-randomized, patient-choice study specifically enrolled depressed adolescents who had attempted suicide in the past 3 months (Brent *et al.* 2009; Stanley *et al.* 2009; Vitiello *et al.* 2009*a*). Youths were treated mainly with SSRI and CBT for 6 months, during which 12% experience another reattempt. Depression, however, improved over time at a rate that was comparable to that observed in non-suicidal depressed adolescents (Vitiello *et al.* 2009*a*). These data suggest that antidepressant treatment can be of benefit to depressed youths at high risk for suicide, but also confirm that suicidal behavior is determined by other factors besides depression and that, improvement of depression *per se*, may not necessarily avert the risk for suicide.

Where do we go from here?

Even from this brief overview, it is evident that a considerable amount of research has been conducted on child and adolescent depression in recent years. This is a significant accomplishment, especially when considering that until the 1980s it was seriously doubted that children could experience depression. Research has shown that depression can indeed be successfully prevented and treated during development. As a consequence, screening of adolescents (12–18 years of age) for major depressive disorder is now recommended in primary care pediatric settings with the purpose of early identification, treatment and possible referral to mental health specialized care (U.S. Preventive Services Task Force, 2009).

However, research has also revealed the limitations of the current treatment approaches, which are on average only modestly effective. The relatively small therapeutic benefit of the available interventions may be in part an artifact of the considerable heterogeneity of the current nosological construct of depression. As discussed, this heterogeneity may be even greater in childhood than in adulthood, because the manifestations of psychopathology are often incomplete during development, with consequent diagnostic uncertainty, for example, regarding possible bipolarity. It seems logical to focus on ways to personalize treatment by trying to identify subgroups of patients more likely to benefit from specific interventions rather than pursue interventions that fit all. While previous efforts to subtype depression go back several decades and have not been successful, novel approaches, possibly trying to integrate multiple types of clinical and genetic information, may offer new perspectives (Fournier *et al.* 2009; Ising *et al.* 2009; Zimmermann *et al.* 2009). Most importantly, it is now evident that any meaningful effort to change the life time trajectory of mood psychopathology and avert the burden of depression must include interventions focused on children and adolescents.

Disclosures

The author reports no financial relationships with pharmaceutical companies during the past 10 years.

The opinions and assertions contained in this report are the private views of the author and are not to be construed as official or as reflecting the views of the Department of Health and Human Services, the National Institutes of Health or the National Institute of Mental Health.

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